IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Martin et al.
Application No. 10/519,311
Filed: December 22, 2004
Confirmation No. 9128
For: METHOD OF TREATING AUTOIMMUNE DISEASES WITH INTERFERON-BETA AND IL-2R ANTAGONIST
Examiner: Bruce Hissong
Art Unit: 1614
Attorney Reference No. 4239-64111-05

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DECLARATION OF DR. ALICE FONG UNDER 37 C.F.R. § 1.132

1. I, Alice Fong, am a medical director in clinical development at PDL BioPharma, Inc. I hold a Pharm.D. degree from the University of California, San Francisco. I completed an internship at St. John's Hospital in Springfield, Il. I have conducted clinical trials for the past 23 years; a copy of my *curriculum vitae* is attached.

2. I have reviewed the pending claims of the above-referenced application, which are directed to treating a subject with multiple sclerosis by administering to the subject a therapeutically effective amount of interferon beta and a therapeutically effective amount of an antibody that specifically binds interleukin-2 receptor, wherein the antibody is administered every other week for two weeks and then monthly, once a week, every other week, or once a month. It is my understanding that claims 1, 3-6, 8-14, 16-17 and 19 are rejected as allegedly being obvious over the "Study for Zenapax" document (htpp://www.ms-network.com/pat/newsflash/show.asp?ID=143), Khoury et al. (Arch. Neurol. 57: 1183-1189, 2000), Paty et al. (Neurology 43: 662-667, 1993) and Jacobs et al. (Ann. Neurol. 39: 285-294, 1996).

3. We have conducted a clinical trial to investigate the effect of concurrent daclizumab and interferon-beta therapy in patients with active relapsing remitting multiple sclerosis (MS). This multi-center, randomized, double-blind, placebo controlled study was performed at 51 sites, both in the U.S. and abroad. A total of 230 patients enrolled in the study. The inclusion criteria were:

(1) males and females, 18-55 years of age

(2) Diagnosis of MS by McDonald criteria

(3) EDSS score of ≤ 5.0

(4) subject on stable interferon-beta regimen for at least six months

(5) subject had at least one MS relapse on interferon beta or a qualifying MRI within 12 months

The patient population was divided randomly into three groups:

(1) daclizumab (Roche Penzberg) at 2 mg/kg subcutaneously every two weeks with concurrent interferon-beta therapy;

(2) daclizumab at 1 mg/kg subcutaneously every four weeks with concurrent interferon beta therapy (a placebo was administered every two weeks, to alternate with daclizumab); and

(3) placebo every two weeks with concurrent interferon beta therapy (control group).

The primary efficacy endpoint was the total number of new or enlarged gadolinium contrast enhancing lesions on monthly brain MRIs between week 8 and week 24 of the study. Serious adverse events (SAEs) were also assessed. A diagram showing the details of the study design is attached as Exhibit A.

Statistical analyses were used to study the efficacy of the treatment regimens. Individuals in Group (1), who received 2 mg/kg daclizumab every two weeks had a 72% reduction ($p=0.004$) in the mean number of new or enlarged gadolinum contrast enhancing lesions as compared to the control group. Individuals in Group (2), who received 1 mg/kg daclizumab every four weeks had a 25% reduction ($p=0.501$) in the mean number of new or enlarged gadolinum contrast enhancing lesions as compared to the placebo control group. Thus, there was a statistically significant reduction in the mean number of new or enhanced lesions in Group (1), who received

2 mg/kg daclizumab every two weeks, and a strong trend in the reduction of Group (2), who received 1 mg/kg daclizumab every four weeks. The extent of this reduction could not have been predicted based on prior results.

In the study population there were 26 patients with 35 SAEs at week 24. About 40% of these SAEs were infections or inflammatory conditions such as esophagitis or cholecystitis. Those SAEs that were assessed as "study drug related" showed the highest frequency with infections (3.9% in the daclizumab treated populations as compared to 0% in the control group). The SAEs that were drug related were highest in Group (1).

The conclusions of the study were that treatment with daclizumab in combination with interferon-beta is more effective than treatment with interferon-beta alone. The preliminary safety profile was within acceptable limits. An abstract describing the results from this study is attached as Exhibit B.

4. The Study of Zenapax describes a study protocol wherein patients will be treated with seven intravenous infusions of Zenapax (daclizumab) over a six month period, and indicates that the subjects will have MRI scans before each infusion. However, one of skill in the art could not have predicted whether daclizumab would have any beneficial effect based on this description. Jacobs et al. and Pary et al. describe the use of interferon-beta to treat MS. Khoury et al. teach that the number of CD25+ T cells is correlated with the gadolinium enhancing lesions in patients with MS. Even if one of skill in the art were to combine the teachings of The Study of Zenapax with Jacobs et al., Paty et al. and Khoury et al., one of skill in the art could not predict the superior results obtained in this clinical trial using the treatment regimens that utilize both daclizumab and interferon-beta.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Alice Fong
Alice Fong, Pharm.D

18 September 2007
Date